PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(date/month/year)* 17 December 2004 (17-12-2004)

Applicant's or agent's file reference	FOR FURTHER ACTION
86356-3/ABA	See paragraph 2 below

International application nº	International filing date *(date/month/year)*)	Priority date *(date/month/year)*
PCT/CA2004/001466	06 August 2004 (06-08-2004)	08 August 2003 (08-08-2003)

International Patent Classification (IPC) or both national classification and IPC

Applicant ULYSSES PHARMACEUTICAL PRODUCTS INC. ET AL

1. This opinion contains indications relating to the following items :

[X]	Box No. I	Basis of the opinion
[ ]	Box No. II	Priority
[ ]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[ ]	Box No. VI	Certain documents cited
[X]	Box No. VII	Certain defects in the international application
[X]	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**
If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/	Authorized officer
Commissioner of Patents *Canadian Patent Office* *Box PCT, Ottawa/Gatineau K1A 0C9* Facsimile No. (819) 953-9538	Yong-Huang Chen (819) 956-4113

Form PCT/ISA/237 (cover sheet) (January 2004)

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language which it was filed, unless otherwise indicated under this item.

[ ] This opinion has been established on the basis of a translation from the original language into the following language __ , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of :

a. type of material

[ ] a sequence listing

[ ] table(s) related to the sequence listing

b. format of material

[ ] in written format

[ ] in computer readable from

c. time of filing/furnishing

[ ] contained in the international application as filed.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority for the purposes of search.

3. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments :

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Box No. II Priority

1 [ ] The following document has not yet been furnished :

[ ] copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

[ ] translation of the earlier application whose priority has been claimed (rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2 [ ] This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purpose of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary :

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of :

[ ] the entire international application

[X] claims Nos. 29-33

because

[X] the said international application, or the said claims Nos. 29-38 relate to the following subject matter which does not require an international preliminary examination *(specify)* :
Although claims 29-33 are directed to a method of treatment of the human/animal body, the examination has been carried out and based on the alleged effects of the compound/composition. Concerning the assessment of industrial applicability of subject-matter relating to therapeutical applications, no unified criteria exist in the PCT. The patentablilty can also be dependent upon the formulation of the claims. CIPO, for example, does not recognise as industrially applicable claims to a method of medical treatment per se, but will allow, however, claims to a new use of a compound either as a therapeutic agent or for manufacture of a medicament in a medical application.

[ ] the description, claims or drawings *(indicate particular elements below)* or said claims Nos. ___ are so unclear that no meaningful opinion could be formed *(specify)* :

[ ] the claims, or said claims Nos. ___ are so inadequately supported by the description that no meaningful opinion

[ ] no international search report has been established for said claims Nos. ___.

[ ] the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that :

the written form	[ ]	has not been furnished
	[ ]	does not comply with the standard
the computer readable form	[ ]	has not been furnished
	[ ]	does not comply with the standard

[ ] the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

[ ] See Supplemental Box for further details.

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Box No. IV Lack of unity of invention

1 [ ] In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has :

[ ] paid additional fees

[ ] paid additional fees under protest

[ ] not paid additional fees

2 [ ] This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3 This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

[ ] complied with

[ ] not complied with for the following reasons :

4 Consequently, this opinion has been established in respect of the following parts of the international application :

[ ] all parts

[ ] the parts relating to claims Nos. ____

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Box No. V reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	2-10, 12-25, 39-42	YES
	Claims	1, 11, 26-28	NO
Inventive step (IS)	Claims	2-10, 12-25	YES
	Claims	1, 11, 26-28, 39-42	NO
Industrial applicability (IA)	Claims	1-28, 39-42	YES
	Claims	29-38	NO

2. Citations and explanations :

1. Cited documents

The following documents are considered to be relevant:
D1 Zhikhareva G.P. et al, "Synthesis and Study of Antiviral Activity of Substituted 4-(d-diethylamino-a-methylbutylamino)-2-styrylquinazolines", Khimiko-Farmatsevticheskii Zhurnal (1978), 12 (11), 44; Chemical Abstracts: 90:121527
D2 US 3973021 A
D3 US 3974277 A
D4 US 3974648 A
D5 US 3542748 A
D6 US 3324122 A

2. Novelty - Article 33(2)

Claims 1, 11 and 26-28 lack novelty under PCT Article 33(2) as being anticipated by D1. D1 teaches 7-chloro-4-(4-(diethylamino)-1-methylbutylamino)-2-(2-(5-nitrofuryl)vinyl)quinazoline as an antiviral agent. This nitrofuran compound falls within the definition of formula 1.0 in claim 1 where R_1 is C_1-C_{10} alkyl and R_2 is hydrogen, in light of the broadened definition of "alkyl" on pages 6-7.

3. Inventive step - Article 33(3)

3.1 Problem to be solved
According to the description on pages 2-3, the problem underlying the application is to provide alternative antibacterial nitrofuran compounds with a wider spectrum of activity, greater potency and particularly more effective against resistant bacterial strains over existing nitrofuran antibacterial agents.
3.2 Closest prior art
D2-D6 represent the most relevant prior art due to the close structural similarity of antibacterial nitrofuran compounds disclosed therein. In D2-D4, the nitrofuran moiety is linked at position 2 to the quinazoline moiety at position 2 through a vinyl group; in D5 and D6, the nitrofuran moiety is linked at position 2 to the quinazoline moiety at position 2 directly.
3.3 Solution objectively provided
Vinyl-linked quinazolinyl nitrofurans of the application demonstrate a wider spectrum of antibacterial activity (see tables 2-4), for example, against *E. coli*, *S. aureus* and *Salmonella* over the closest prior art in D2-D4 and as well as effectiveness against bacteria multiply resistant to antibacterial agents in current use (see tables 5-7). The effect of halogen substitution is significant enough that further modification with a methyl piperidinyl group in the neighbouring position can be sustained without loss of the widened antibacterial spectrum and effectiveness against multiply resistant bacteria.
3.4 Evaluation of the solution to the problem
The principal structural feature shared among the quinazolinyl nitrofurans lies in the halogen (specifically fluorine) substitution at positions 6 and/or 7 of the quinazoline moiety. Although D5 and D6 teach that directly linked quinazolinyl nitrofurans are active against *E. coli*, *S. aureus* and *Salmonella*, they are silent about effectiveness against multiply resistant bacteria. The improvement in antibacterial performance resulting from this modification is therefore neither taught nor expected from the prior art. Thus, the novel subject matter of claims 1-38 involves an inventive step. (see comments below for industrial applicability)

4. Industrial Applicability - Article 33(4)

Claims 29-33 relate to a method of medical treatment. Concerning the assessment of industrial applicability of subject-matter relating to therapeutical applications, no unified criteria exist in the PCT. The patentablilty can also be dependent upon the formulation of the claims. Canadian Intellectual Property Office , for example, does not recognise as industrially applicable claims to a method of medical treatment per se, but will allow, however, claims to a new use of a compound either as a therapeutic agent or for manufacture of a medicament in a medical application.

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Box No. VI **Certain documents cited**

1. Certain published documents (Rules 43*bis*.1 and 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*

2. Non-written disclosures (Rule 43*bis*.1 and 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

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Box No. VII Certain defects in the international application

The vague and imprecise statement in the description on page 40, final paragraph, implies that the subject matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity of the claims pursuant to Article 6 when used to interpret them. This statement should be therefore amended to remove this inconsistency.

A statement in an application, such as found on page 1, line 5 and page 40, line 26, which incorporates by reference any other document, causes uncertainty concerning whether all the information required for the understanding and working of the invention is included in the filed description, pursuant to PCT Rule 5.1(a)(iii). A patent specification should be self-contained and capable of being understood without reference to other document pursuant to PCT Guideline 4.26.

The following clerical errors were found:
1) the format of indicating MIC range in the "TMP-SMX" column of Table 7 is inconsistent with the rest of the table;
2) in Figure 3, "compound Example I" in figure title and "example I" in figure legends should read "Compound V (Example I)" and "Compound V" respectively.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

Claim 1 lacks clarity pursuant to Article 6 for being directed to the desired result rather than to the combination disclosed to achieve that result. The functional term "solubilizing group" in claim 1 is non-limitative in structure and it is uncertain what structural features are supposed to increase solubility.

Claims 1-5, 9, 11-18 and 26-38 do not meet the criterion set out in Article 6 for not being fully supported by the teaching of the description. The functional term "solubilizing group" in claim 1 is non-limitative in structure and embraces an infinite number of possibilities not yet explored by the applicant. Obviously, the structural formula 1.0 in claim 1 encompasses possibilities, which are not regarded as obvious modifications of the examples given in the description. Further, the increase in aqueous solubility as illustrated on page 40 does not have manifested therapeutic utility from the evidence provided. The fact that compound XV has much inferior performance in all antibacterial assays presented further raises the question of having a "solubilizing group" in positions 6 or 7 regardless of factors such as size and charge. The applicant should either limit the claims accordingly or else provide convincing arguments and/or evidence showing that the entire claimed range has the same antibacterial activity.

Related to the objection above is the question of disclosure concerning how to make nitrofurans of formula 1.0 possessing any solubilizing group. Since the "solubilizing group" is not structurally defined, there is no way of assessing the feasibility of synthesis on basis of the description. Therefore, claims 1-5, 9, 11-18 and 26-38 do not meet the criterion set our in Article 5 for insufficient enablement.

Claim 18 lacks clarity pursuant to Article 6. The term "substituted", is non-limitative and renders the claim obscure in scope without further definitive qualification about identity and number of atoms involved.

Claim 26 does not meet the criterion set out in Article 6 for not fully and explicitly defining a composition in terms of its constituent elements. A composition should contain at least two ingredients. In the instant claim, a pharmaceutically acceptable carrier should be explicitly indicated.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of :